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### Preventing injury in childhood

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## Vitamin A supplements in newborns and child survival

Benefit depends on the setting, baseline infant mortality, and vitamin A deficiency



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### RESEARCH, p 1416

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Vitamin A supplementation at 6-72 months of age has become a mainline intervention for improving survival in populations with endemic vitamin A deficiency.<sup>1</sup> However, in the same setting, supplementation at 1-6 months of age has little or no effect on mortality, whether given with immunisation or not.<sup>2-3</sup>

Giving vitamin A supplements to newborns within the first few days of life significantly reduced early infant mortality in Asian populations with endemic maternal vitamin A deficiency and high infant mortality.<sup>4,6</sup> In Africa, however, this strategy had no beneficial effect on early infant survival in an urban setting<sup>7</sup> or—as reported in the accompanying paper by Benn and colleagues—in a peri-urban setting.<sup>8</sup>

How can these findings be reconciled? A meta-analysis of all the newborn dosing studies might provide a more accurate estimate of the true effect on early infant mortality. But combining these studies would be a fundamental mistake, because the variation in effect on early infant mortality in the five available studies is what would be expected given the variations in the populations included.

So how can the variation in outcomes be explained? Differences between the study populations are key. Vitamin A supplements have the greatest benefit in populations with high mortality and endemic vitamin A deficiency. Deaths from causes (such as infectious diseases) that are most likely to be affected by vitamin A supplements will already be low in populations with low mortality. Also, if a population is already receiving sufficient vitamin A from dietary sources, supplements are unlikely to improve vitamin A status enough to decrease death from infectious diseases.

So, which of the five studies of vitamin A dosing in newborns were conducted in populations with high infant mortality and endemic vitamin A deficiency? The studies in India and Bangladesh were done in populations with high infant mortality.<sup>5-6</sup> In these studies, rates of maternal night blindness in pregnancy were high enough to classify vitamin A deficiency as being of public health importance.<sup>6,9</sup> In contrast, both African studies were done in populations with little, if any, vitamin A deficiency; mortality in the Zimbabwean study was very low<sup>7</sup>; and the study in Guinea-Bissau reduced mortality by excluding the highest risk infants (those with low birth weight) and giving free care and drugs to sick infants.<sup>8</sup>

Vitamin A status in newborns is difficult to interpret because all infants are born with low reserves of vitamin A, especially those born prematurely. Newborns depend on adequate supplies from breast milk or

appropriate substitutes to satisfy physiological demands in early life.<sup>10</sup> The risk of vitamin A deficiency in these cases should be judged by the status of the mothers, not the infants. Despite Benn and colleagues' claim that differences in the characteristics of the study populations cannot explain the variation in treatment effects, they are the most likely explanation.

The outlier study in this assessment is the Indonesian study, the smallest of the five studies. It found that giving vitamin A supplements to newborns had a large effect on early infant mortality, even though the mothers' serum retinol concentrations were relatively normal.<sup>4</sup> But vitamin A deficiency is a common problem in women and children in Indonesia,<sup>11</sup> and liver reserves may have been low even though serum retinol concentrations were adequate; alternatively, the finding in Indonesia may have been the result of chance.

Benn and colleagues' study provides no new information on the interactions between vitamin A supplements and vaccines as all children received concurrent BCG and, we assume, the other standard vaccines including diphtheria, pertussis, and tetanus; oral polio; hepatitis B; and measles vaccines. Observational evidence suggests that giving vitamin A supplements to infants may modify the effect of vaccines on early infant mortality.<sup>12</sup> However, little is likely to be gained from further observational data as the selection bias associated with the receipt of vaccines is almost impossible to overcome. Further delineating this interaction will require randomised trials of both newborn vitamin A supplementation and immunisation, which are unlikely given current immunisation policies.

Still missing from the evidence base are trials from populations in sub-Saharan Africa with endemic vitamin A deficiency and high infant mortality. Such populations exist in areas of eastern and southern Africa, and trials in these areas are urgently needed. Also, we still do not know why vitamin A supplements are beneficial when given in the first few days of life, at least in Asia, but have no effect on mortality when given only a few weeks later at the time of the first diphtheria, pertussis, and tetanus immunisation. Studies exploring the mechanisms of action of early versus later supplementation would be helpful.

Given current evidence, Benn and colleagues' conclusion that “a global or regional recommendation of 50 000 IU vitamin A supplementation at birth is unwarranted” is untenable. For populations in Asia who are deficient in vitamin A the evidence for benefit is convincing. Recommendations for Africa await the

results of trials conducted in appropriate populations.

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## Risk factors for gastroschisis

Genitourinary infection in early pregnancy can be added to the existing list

### RESEARCH, p 1420

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Gastroschisis is a small abdominal fissure lateral to an intact umbilical cord, generally to the right. The bowel herniates throughout the fissure and is not covered by membrane. Unlike most other birth defects, reported rates of gastroschisis have increased over the past 25 years from 0.1-1.0 per 10 000 births to 3.0-5.0 per 10 000 births in many developed and developing countries, with the notable exception of Italy, where rates have remained stable at under 1.0 per 10 000.<sup>1-3</sup> In the linked study, Feldkamp and colleagues assess whether genitourinary infections increased the risk for gastroschisis in participants in the national birth defects prevention study (NBDPS).<sup>4</sup>

Research on risk factors has previously been hampered by the relative rarity of the defect and by unclear case definition. For example, the ICD-9 (international classification of diseases, 9th revision) coding system combined omphalocele and gastroschisis under a single code (756.7). Moreover, the pathogenesis and the embryological period during which the defect develops are still unclear. The debate about whether gastroschisis is a disruption occurring after the formation of the abdominal wall or a primary malformation of the folding process of the abdominal wall has recently reopened.<sup>5</sup>

Nevertheless, one consistent risk factor has been shown in all epidemiological studies, young maternal age. One European study found that compared with mothers aged 25-29, the relative risk was 7.0 (95% confidence interval 5.6 to 8.7) for mothers under 20 and 2.4 (2.0 to 3.0) for mothers aged 20-24 years.<sup>3</sup> The correlation with young maternal age suggests that environmental factors are involved.

In their case-control study, Feldkamp and colleagues assess the association between gastroschisis and genitourinary infection from one month before conception through to the end of the first trimester.<sup>4</sup> Diagnosis was by expert review of all cases in live born infants, stillbirths, and terminations of pregnancy. The study uses a computer assisted telephone interview in English or

Spanish as part of an ongoing population based study funded by the Centers for Disease Control and Prevention, which includes 10 state run surveillance systems of birth defects in the United States. A genitourinary infection was self reported by 16.2% of women with affected infants (n=505) and 8.7% of mothers of healthy live born infants (n=4924). The resulting odds ratio—adjusted for maternal age, body mass index before conception, smoking, and Hispanic ethnicity (a specific genetic background and suggestive of a low socioeconomic status)—was 1.5 (1.1 to 1.9).

The study is important not only because it highlights genitourinary infection as a new risk factor for gastroschisis, but also because the risk factors used in the logistic model to compute adjusted odds ratios were found to be important in previous studies.<sup>6</sup> For example, a recent large population based case-control study in the United Kingdom found significant adjusted odds ratios for the use of aspirin (20.4), use of vasoconstrictive recreational drugs (ecstasy, amphetamine, and cocaine) (3.3), history of gynaecological infection (2.6), use of any recreational drug (2.2), low body mass index (2.0), unmarried status (1.8), and cigarette smoking (1.7).<sup>7</sup> If the associations are causal, the highest population attributable risk is for cigarette smoking (28%); this information is useful for promoting preventive action.

Other case-control studies have indicated that having at least two children, each from a different father, is a further risk factor.<sup>8</sup> An increased risk of gastroschisis has been reported in women who smoke cigarettes or marijuana (26.5, 7.9 to 89.4) and women with a low body mass index.<sup>9</sup> An interaction between smoking and gene polymorphisms (*ICAM-1* gly241arg, *NOS3* glu298asp, *NPPA* T22238C) has also been suggested.<sup>10</sup>

The overall pattern of findings from all of these studies suggests that the risk for having an infant with gastroschisis is highest in young women, mainly teenagers, with one or more of the following characteristics—have low socioeconomic status, smoke

cigarettes, eat too little, drink alcohol, use illicit drugs, have early and unprotected sexual intercourse, and have genitourinary infection.

These risk factors—perhaps in combination with genetic susceptibility—may explain the link between low maternal age and increased frequency of the defect in many countries. But to explain the threefold to fivefold increase seen in many countries in the past few decades, several risk factors must strongly interact.

The study by Feldkamp and colleagues provides an opportunity to evaluate the current interacting web of risk factors.<sup>4</sup> Moreover, it is interesting that 43% of mothers with affected infants reported a *Chlamydia trachomatis* infection because this infection has many common risk factors with gastroschisis, plus it can be screened for and treated.<sup>11</sup> Ascertaining a history of *C trachomatis* infection should be considered in future studies.

In the meantime, preventive actions to reduce the frequency of gastroschisis worldwide must be considered and urgently implemented. Global reproductive health counselling, which involves several preventive actions tailored to the needs of adolescents and young women, is the best approach to deal with the complex biomedical and sociocultural set of risk factors.<sup>12</sup>

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## Wheeze in preschool children

### Exercise induced wheeze and atopic disorders predict persistent asthma

#### RESEARCH, p 1423

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Wheeze is an increasingly common symptom in preschool children. In Leicestershire, the proportion of children aged less than 5 years who had ever wheezed rose from 16% in 1990 to 29% in 1998.<sup>1</sup> Wheezing illness is therefore a common source of anxiety to parents and professionals involved in the care of young children, all of whom would like an accurate diagnosis and prognosis. In the accompanying study, Frank and colleagues report the long term outcome of 628 children with and without preschool wheeze, including factors that predict asthma in later life.<sup>2</sup>

Many different wheeze phenotypes have been described in this age group.<sup>3-4</sup> Most children will eventually turn out to have been “transient early wheezers.” These children do not usually have a family history or personal history of atopy, and the wheeze tends to settle by the age of 3 years. A second group of children with transient symptoms consists of “non-atopic wheezers,” most of whom settle by the age of 5 years, although the syndrome can persist well into school age years (figure).<sup>5</sup>

These two groups overlap considerably; infection is the main precipitant of wheeze in both, so they are often lumped together as having “virus associated wheeze” or “wheezy bronchitis.” These two groups can be distinguished by pulmonary function measurements—the transient early wheezers have relatively narrow airways that are readily obstructed by the minor degree of mucosal inflammation that accompanies upper respiratory tract

infection, whereas the non-atopic wheezers show bronchial hyper-reactivity to methacholine.<sup>4</sup> These assessments are unlikely to be available to clinicians working outside tertiary centres, however.

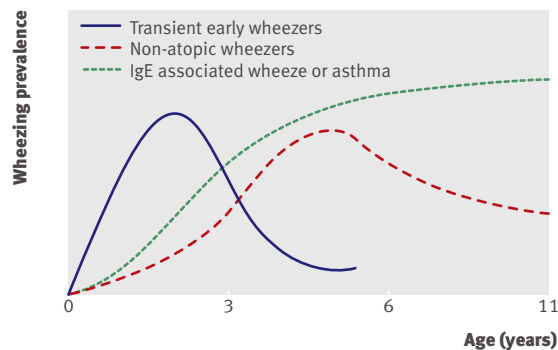
A third group—“IgE associated wheeze”—is important because wheeze tends to persist in these children and a diagnosis of asthma can reasonably be offered. It is defined in terms of objective measures of atopy—that is, raised IgE concentrations, positive radioallergosorbent tests, or positive skin prick tests.<sup>4</sup> This type of wheeze is also associated with evidence of airway inflammation in the form of raised exhaled nitric oxide concentrations.<sup>6</sup>

Faced with a wheezing toddler or infant, what should clinicians do? Firstly, it must be established that wheeze is actually present. The public's understanding of the term wheeze seems to have changed. This term should be reserved for whistling noises, but it is now being used to describe various vibratory phenomena.<sup>7</sup> Mindful of these problems, in a birth cohort study in Aberdeen, we identified 210 parents who described their 2 year old children as having wheezed; of these, only 24 (11%) defined this wheeze as whistling in character, the others described it as a rattling or purring noise.<sup>8</sup> Parental use of the word wheeze must therefore be viewed with suspicion.

Parents will have little interest in the taxonomy of wheezing disorders but will want to know about treatment and prognosis. In terms of treatment, the efficacy of  $\beta_2$  agonists during infancy is still unclear,<sup>9</sup> but they are



**Prevalence of wheeze phenotypes in childhood; these groups are by no means mutually exclusive, and considerable overlap occurs. Adapted, with permission, from Stein et al<sup>4</sup>**



generally effective in older children, particularly if given by means of a holding chamber (spacer) and mask.<sup>10</sup> Inhaled corticosteroids are of little benefit in intermittent virus associated wheeze and are best reserved for children with more frequent or severe symptoms, particularly if there is a personal or family history of other atopic disorders, positive skin prick tests, or biochemical evidence of atopy.<sup>11 12</sup>

Until now it has been difficult to provide prognostic information on individual children, but Frank and colleagues' study helps by assessing the predictive value of simple clinical data rather than complex immunological and physiological tests.<sup>2</sup> The authors examined several factors that might influence the prognosis of wheeze in early childhood. Surprisingly, the severity and frequency of symptoms were unrelated to the persistence of symptoms. In contrast, a history of exercise induced wheeze—a clinical manifestation of bronchial hyper-reactivity—and a history of atopic disorders strongly predicted persistence (exercise: odds ratio 4.44, 95% confidence interval 1.94 to 10.13; atopy: 3.94, 1.72 to 9.00). These findings support the traditional view that asthma is essentially the occurrence of these two traits in the same person.

Obviously, it could be argued that these results are exactly what might have been anticipated—the more it

looks like asthma, the more likely it is to be asthma—but most clinicians would probably have expected the frequency and severity of attacks to have had some bearing on prognosis. This study therefore provides the clinician with a simple approach to prognosis in the wheezy pre-school child using information that is easily acquired at the bedside or in the consulting room. Nevertheless, the confidence intervals surrounding these adjusted odds ratios are quite wide (and in the case of male sex include unity), so the approach should be used as a guide rather than a formula for certainty.

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## Preventing injury in childhood

Injury surveillance in the UK lags behind other European countries

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UK Child Safety Week will be launched by the Child Accident Prevention Trust on 23 June this year. Its aim is to raise awareness of childhood accidents and prevention strategies.

Unintentional injury accounts for around one in five of all deaths in children and adolescents in the European Union with the highest injury rates occurring in Greece, Estonia, and Belgium.<sup>1</sup> In the United Kingdom, unintentional injury is a leading cause of death and illness in children and is the most common cause of hospital admission—it accounts for around two million visits to accident and emergency departments each year, at a cost to the NHS of around £146m (€182m; \$288m).<sup>2</sup> Injury in childhood is strongly associated with poverty, and death rates from unintentional injury in the UK are around three

times higher in children from the poorest families than in those from the least poor families; little is known about this topic in other countries.<sup>3-5</sup> Children of parents in the UK who have never worked or who are long term unemployed are 13 times more likely to die from unintentional injury and are 37 times more likely to die as a result of exposure to smoke and fire than children of parents with higher managerial and professional jobs.<sup>2</sup>

Most injury is avoidable. For example, if Scotland matched Sweden in death rates for children and adolescents from unintentional injury then 62 lives a year—more than 40% of the total lives lost—would be saved.<sup>1</sup>

Injury surveillance systems are essential for monitoring risk and developing and evaluating community based

initiatives aimed at preventing injury in children. They can motivate policy makers and communities to participate in prevention activities.<sup>6</sup> However, like many countries in Europe, the UK has no comprehensive surveillance system for documenting childhood injury, so the causes, risk factors, and short term and long term consequences of injury are unknown. This hinders development and implementation of evidence based strategies to prevent injury.

The Audit Commission, Healthcare Commission, and the European Child Safety Alliance have criticised the fragmented nature of injury policy in the UK and the lack of progress in setting up geographical population based surveillance systems. The UK Department of Trade and Industry's surveillance system of accidents at home and leisure (based on hospital samples) was discontinued in 2002. Wales is the only UK country that routinely surveys injuries in children in accident and emergency departments using the All Wales Injury Surveillance System.<sup>7</sup> Scotland is the only UK member of the "EuroSafe" Child Safety Action Plan project under the European Commission's Public Health Programme, which aims to "enhance child and adolescent safety by increasing awareness of the injury issue and uptake of proven prevention strategies." However despite the pioneering work of the Information Services Division (NHS Scotland), which has incorporated the World Health Organization's international classification of external causes of injuries into the National Clinical Dataset Development Programme, Scotland has yet to identify the resources to develop and implement a surveillance system in NHS accident and emergency departments.

Part of the difficulty is that responsibility for children is shared across numerous sectors and agencies. So what should be done? The Accidental Injury Task Force, which advised the chief medical officer in England on how to reduce the rates of death and serious injury from accidents, recommended that public health observatories and their counterparts in local government should play a key role in injury surveillance. The public health observatories have established a virtual Injury Observatory of Britain and Ireland—which acts as a central resource for data on injuries, prevention strategies, and collaborative work—but little political support exists to develop the surveillance systems required to monitor childhood injury at country level.

Around one in five non-fatal unintentional injuries in children result from sport or recreational activities and almost a third occur in places used for sport, play, or recreation.<sup>8</sup> The government hopes that the billions of pounds being invested in the 2012 Olympics and paraolympics will help reverse the decline in physical activity and fitness and the high levels of childhood obesity. However, the benefits have to be weighed against the risks—more than half the benefits of physical exercise may be lost through injuries, which can result in sports activity being abandoned completely.<sup>9</sup>



ROBERT DANT/ISTOCK

Injury surveillance systems and prevention strategies could be used to help children participate in "safe" sport and reduce inequalities in rates of injury across social classes. Sweden, the Netherlands, and Denmark have developed well established population injury surveillance systems to inform intervention and prevention strategies.<sup>10</sup> All three countries have the lowest mortality from unintentional injury in children and adolescents in Europe<sup>1</sup> and high levels of participation in sport—Sweden has the highest rate of participation in Europe and half the levels of obesity seen in the UK.<sup>11 12</sup>

For UK governments to improve the health and wellbeing of children and to reduce inequalities, much more is needed. The creation of a UK all party parliamentary group to champion the cause of accident prevention is a small beginning. UK Governments must now find the resources to develop population based injury surveillance systems so that the true incidence, causes, risk factors, and long term sequelae of injuries can be used to inform evidence based intervention.

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# Health and wealth in Europe

European initiative seeks to spur action to tackle widening health divides

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Next week, health ministers from all 53 member states of the World Health Organization's European Region will meet in Tallinn to agree on a new charter. The first pan-European charter on health systems—signed in Ljubljana in 1989—focused on the purpose, goals, and core values of health systems. The Tallinn charter is more ambitious. Its aim is to spur political recognition of the economic case for investing in health systems, and to promote more effective stewardship of health resources by governments.

Expenditure on health services is still widely viewed as a short term cost, but substantial evidence now exists that it can benefit the economy. According to WHO, increasing life expectancy at birth by 10% increases economic growth by 0.35% each year.<sup>1</sup> The view that health and wealth go together was also at the heart of the Wanless report, which argued that putting a high priority on disease prevention and effective early treatment would reduce future health-care costs.<sup>2</sup> Former European Union Commissioner for Health and Consumer Protection, David Byrne, argued for positioning health as a driver of economic development—an approach reflected in the new EU health strategy.<sup>3</sup> A similar case has been made for eastern Europe and central Asia.<sup>4</sup> Globally, the Commission on Social Determinants of Health, whose final report will appear this summer, has stated that good health enables people to participate in society, with potentially positive consequences for economic performance.<sup>5</sup>

Not all countries accept the case for investing in health. This is particularly true among those European countries with the poorest health statistics. Disparities in wealth and health within the WHO European Region are wide. WHO data from 2004 showed that gross domestic product per capita ranged from less than \$2000 (£1000; €1300) in Tajikistan to over \$35 000 in Norway, and that the percentage of total government spending allocated to health varied from about 4% to 18%. Inequalities in mortality may be small in some southern European countries, but they are large in most countries in the eastern and Baltic regions.<sup>6</sup> Within Europe, the United Kingdom's record is not one to be proud of. Life expectancy of men in one of the most deprived areas of Glasgow is 54 years compared with 82 years in the most affluent areas of the town.<sup>7</sup> Furthermore, inequalities in health are continuing to grow across Europe.<sup>8</sup>

Increased investment in health will pay dividends only if it is well spent. The charter underlines the notion that governments must improve transparency and accountability for health spending and ensure that spending is aligned effectively to agreed policy objectives. Much hangs on the nature of these policies. According to experts from the WHO European Office, some of Europe's poorer countries—including Moldova and Kyrgyzstan—have tackled inefficiencies

in Soviet era systems they inherited, which has in turn enabled them to improve the coverage and quality of their health services. Others—including Armenia, Azerbaijan, Georgia, and Tajikistan—faced such severe constraints on public spending on health during the 1990s that their systems became highly dependent on private spending. The result has been an increase in health inequalities, with more people impoverished through having to pay for health care. These countries face major challenges in meeting the objective of providing universal access to high quality primary healthcare services.<sup>9</sup>

The need to improve the performance of health systems and manage limited resources effectively is equally important in rich countries. A promising reform in Germany has seen the government provide insurers with financial incentives to enrol people with chronic disease into disease management programmes. In Switzerland, governance and funding have not been well aligned, and some cantonal governments have had to “rescue” loss making hospitals. Evidence from all countries reaffirms the importance of universal coverage, disease prevention and health promotion, organisational efficiency, high quality service delivery, and interventions aimed at tackling the social determinants of health. For each of these, health systems should measure and aim to improve performance.

Adopting a wider approach to health requires strong, joined up government, which all countries—regardless of their state of development—struggle to achieve; as Wanless concluded, health policy remains stubbornly rooted in health care and in treating the sick. By introducing the “health in all policies” approach, the European Commission has sought to institutionalise a wider approach to health in the development of public policy in all areas, including finance, agriculture, education, housing, transport, and the environment.<sup>10</sup> It is now mandatory to carry out health impact assessments in the course of developing new community policies. Evidence on the effect of health impact assessment is limited but suggests that it can be effective in influencing decisions in sectors outside health. A great deal depends on the seriousness with which it is taken by governments.<sup>11</sup> A key message in the charter is that health ministers must assume a more active advocacy role in getting other ministers to take health seriously.

It is easy to be cynical about the value of grandiose pan-European charters and wrong to assume that economic development will inevitably improve health outcomes and reduce health inequities. The hope behind the Tallinn charter is that it will galvanise the political will to develop more efficient and effective health systems, which are committed to narrowing Europe's massive health and wealth divides.

All references are in the version on bmj.com